REMARKS

Upon entry of this response, claims 1-28 are still pending in the application. Claim 1 is an independent claim drawn to a micro or nano-particulate drug composition, with claims 2-17 depending therefrom, while claim 18 is an independent claims drawn to a method of making a mirco or nano-particulate drug. The remaining claims (claims 19-28) depend from claim 18. Claims 1 and 18 have been amended to clarify the present inventive subject matter. Support for the claim amendments may be found throughout the specification as originally filed. Thus, Applicant submits that no new matter within the meaning of 35 USC 132 is added by the amendments to the claims.

Claims 1-28 stand rejected as obvious over U.S. Patent No. 6,197,349 to Westesen et al. (the '349 patent).

Applicant respectfully traverses this rejection and respectfully request reconsideration and withdrawal thereof. The amendments to the claims and the following remarks are made in order to place the application in condition for allowance.

Rejection of Claims 1-28 Under 35 U.S.C. 103(a)

Claims 1-28 stand rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,197,349 to Westesen et al. (the '349

patent) for the reasons set forth in the Office Action.

RESPONSE

Applicant respectfully traverses this rejection and requests reconsideration and withdrawal thereof.

The reference of record, Westesen et al., does not teach or suggest Applicants' inventive subject matter as a whole, as recited in the claims. Further, there is no teaching or suggestion in this reference which would lead the ordinary skilled artisan to modify the reference to derive the subject matter as defined in the amended claims.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016,

1023 (Fed. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

A. The Present Inventive Subject Matter

As amended herein, independent claim 1 is drawn to a micro- or nano-particulate drug composition comprising a surfactant-drug substance matrix at a temperature above said matrix's melting temperature, said matrix comprising a drug substance and a surfactant, and wherein said surfactant is miscible with said drug substance and does not chemically bond with said drug substance; and wherein said drug composition further comprises micro or nano-sized crystals of said drug substance coated with said surfactant at room temperature, said crystals formed while said matrix is cooled to room temperature under a shearing force.

Likewise, amended independent claim 18 is drawn to a method of

making a micro and nano-particulate drug, the steps comprising: providing a drug substance-surfactant mixture; melting the mixture at a temperature above the mixture's melting temperature; and cooling the mixture under high shear to approximately room temperature, wherein crystals precipitate coated with said surfactant during crystallization.

The remaining claims depend from either claim 1 or 18, and therefore contain all of the limitations found therein.

B. The Prior Art

As has been previously stated, Westesen et al. (U.S. Patent No. 6,197,349) disclose particles comprising a supercooled melt of a poorly water-soluble substance and a stabilizing agent. The particles have a mean particle size of between 30 and 500 nm and disperse compositions containing them as delivery vehicles.

C. Differences Between Claimed Inventive Subject Matter and Cited Prior Art

As an initial matter, Applicant would like to provide a general description of the present inventive subject matter. Applicant has invented a novel drug composition that comprises

micro- or nano-particulate crystals of the drug with a surfactant coated thereon. The inventive drug compositions comprise a drug substance-surfactant matrix when the drug and surfactant are heated to a temperature above the matrix's melting point. The matrix is then cooled under shear to room temperature, allowing the micro- or nano-**crystals** to form. The **crystals** so formed **are of the drug, with the surfactant coated thereon.** The cooling **does not need to be super-cooling, or necessarily even rapid cooling,** in order for the crystals to form. It is the combination of cooling the matrix to room temperature, **while at the same time subjecting the matrix to a shearing force,** that results in the inventive **crystalline** product being formed. **The shearing force provides nucleation sites for the crystals to grow,** and that is why it is important for the shearing force to be present while cooling the matrix to room temperature.

As can be seen above, claim 1 has been amended to better clarify the inventive subject matter and more clearly claim these concepts. Amended claim 1 is now drawn to a drug composition comprising a drug substance-surfactant matrix at a temperature above the matrix's melting point. The matrix comprises the drug substance and the surfactant. At room temperature, the drug composition comprises crystals of the drug coated with the

surfactant. The crystals are formed by cooling the matrix to room temperature while subjecting the matrix to shearing force. The shearing force creates many nucleation sites, thereby **allowing the crystals of the drug to grow with the surfactant coating the crystals as they grow.**

Further, claim 18 has been amended to clarify the method used to obtain the inventive drug compositions. In particular, claim 18 now makes it clear that the resulting product is a crystalline product, and not a non-crystal or amorphous product.

Applicant again states that, "using this process, micro- and nano-particulate drug crystals will form coated with surfactant during the crystallization process. **If cooling does not occur under high shear until the mixture is cooled to at or around room temperature, crystals will grow on the exterior of the surfactant. Surfactant with crystals on the exterior have very poor dissolution.**" (page 21, lines 2-11). Emphasis added. Thus, the inventive aspects of the present claims require **cooling under high shear** in order to obtain a **crystal** product with proper dissolution properties. Applicant respectfully submits that the '349 patent does not disclose these limitations, and there would be no motivation for a skilled artisan looking at the patent to do so.

The Examiner reiterates the argument that the '349 patent

discloses the limitations of the claimed subject matter. In particular, the Examiner indicates that the patent teaches "preparing a dispersion of water-insoluble drug with a stabilizer (such as surfactants), which is then emulsified above the melting point of the substance or mixture of substances (col. 10, lines 1-26) and then subject to vortexing (which reads on shear force) resulting in fine particle preparation." (Page 2 of the office action). However, a careful reading of the '349 patent fails to reveal **any discussion regarding cooling a mixture under high shear force, thereby forming nucleation sites for growing the drug crystals with surfactant coating thereon.** The citations made by the Examiner discuss the vortexing of the mixture for emulsification and/or predispersion, but there is **no discussion regarding cooling the mixture under high shear force in order to create nucleation sites for growing crystals**. In fact, the '349 patent discusses the formation of amorphous, or non-crystalline, drugs, and therefore **there is no need for nucleation sites to be present in the '349 patent.** Particularly, the '349 patent makes it clear that "the particle core of PSMs (particles of supercooled melts) consists of one or more poorly water-soluble substances which are primarily present in an **amorphous, non-crystalline state, preferably as a supercooled melt.**" (col. 8, ll. 43-46, emphasis

added). Thus, Applicant respectfully submits that the product obtained by the method in the patent **will not be the same as the claimed product**, since the '349 patent results in a non-crystalline product and the present invention results in a crystalline product as a result of the formation of the nucleation sites due to the shearing force. As such, Applicant submits that the Examiner has failed to show that the reference teaches each of the claimed limitations.

In addition, Applicant again respectfully submits that one of ordinary skill in the art would not be led by the '349 patent to attempt cooling the mixture under high shear. As is stated above, the vortexing of the mixture in the '349 patent is done **to achieve emulsification of the mixture**, and therefore is done at high temperatures. No mention is made in the patent regarding the need to continue applying a high shear rate **as the mixture is cooled**, since the emulsification takes place at a higher temperature. Therefore, there is no motivation for a skilled artisan to continue applying the high shear rate as the mixture is cooled.

Therefore, Applicants respectfully submit that the '349 patent fails to teach each and every claimed limitation in the independent claims (and also the dependent claims), and that there is no motivation within the patent to modify it in an attempt to achieve

the presently claimed subject matter. Thus, the Examiner has failed to meet the burden of proving a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims as being obvious over the '349 patent.

CONCLUSION

In view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the all pending rejections, and to allow all of the claims pending in this application.

If the Examiner has any questions or comments regarding this matter, he is welcomed to contact the undersigned attorney at the below-listed number and address.

Respectfully submitted,
NATH & ASSOCIATES

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